

REMARKS

1. Disposition of Claims

Claims 25-36 have been added and Claims 1, 3-7, 9-16, and 21-24 have been canceled as being drawn to non-elected subject matter. Accordingly, Claims 2, 8, 17-24 and 25-36 are pending examination. No new matter has been added by this amendment. Reexamination and reconsideration of the application, as amended, are respectfully requested.

2. Compliance With 35 U.S.C. § 103

The Examiner has maintained her rejection of Claims 2, 8, and 17 as allegedly being obvious under 35 U.S.C. § 103 in view of Westaway et al. (USP 6,893,866) and/or Khromykh & Westaway, J. Virol. 71: 1497 (1997), in view of Polo et al., J. Virol. 71: 5366 (1997).

USP 6,893,866 described construction of subgenomic replicons of flavivirus Kunjin and their packaging into virus-like particles by a packaging cell line. Khromykh & Westaway 1997 published construction of subgenomic replicons of flavivirus Kunjin. Polo et al. 1997 described the preparation of a stable *full-length* cDNA copy of flavivirus dengue virus type 2 RNA capable of producing an infectious RNA transcript in vitro. The Examiner argues that it would have been obvious to modify the infectious RNA system of Polo et al. to create a subgenomic replicon by gene deletion as taught for the analogous Kunjin virus with a reasonable expectation of success (OA mailed 9/17/2007, page 5). Applicants respectfully disagree.

The Examiner's rationale disregards the known differences between the stability of the dengue viruses and other flavivirus family members. Polo teaches that artisans at the time had no effective means for efficiently producing dengue virus because of its instability in traditional cloning systems, such as *E. coli*. Thus, Polo, et al. discovered that full length dengue virus type 2 could be grown in yeast, or in bacteria using a yeast shuttle vector. However, one of ordinary skill in the art would not believe that deletion mutations of the structural genes from dengue virus could be made without affecting the stability or intracellular replication of the virus.

As recited at para [117], deletion of the E gene by itself yielded no detectable expression of virus proteins, again reinforcing the fact that one cannot predict which mutations within dengue virus would produce an active subgenomic replicon. Applicants have modified the

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claims to remove reference to replicons that only have a deletion of the E gene in order to clarify their invention.

In addition to the unpredictability of making viable dengue replicons, Applicants have unexpected results which rebut the Examiner's argument that the claims are *prima facie* obvious. Applicants unexpectedly discovered that dengue virus mutants with deleted pre-M and E genes (Δ ME), along with mutants with deleted pre-M, E and C genes (Δ CME) are able to replicate *in vitro* for over eight days. Previously, the longest replication of flavivirus replicons without selection was 72 hours (spec. para [0120]). This result was not expected, based on prior experience with other flaviviruses, including Kunjin. This unexpected result means that vaccines using such dengue deletions would be more effective because the viral particles would be able to replicate within the host for a longer period of time, and thus cause a greater immune reaction.

Claim 16 was rejected as being unpatentable over Khromykh in view of Polo et al. and Fields, optionally in view of Westaway et al. (USP 6,893,866). This claim has been cancelled, thus obviating this rejection.

Claims 18-20 were rejected as being unpatentable over Westaway et al. (USP 6,893,866, see also WO 99/28487 of which the USP is a continuation application), in view of Polo et al., J. Virol. 71: 5366 (1997), optionally in view of Khromykh & Westaway, J. Virol. 71: 1497 (1997).

For all of the reasons discussed above, amended Claims 18-20 would not be obvious in view of Westaway and Polo. The Examiner has failed to make a *prima facie* case of obviousness in view of the unpredictability in working with dengue. Moreover, even if such a *prima facie* case was made, Applicants unexpected results rebut any such finding of obviousness. Accordingly, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103 and allowance of the pending claims

3. Double Patenting

The Patent Office provisionally rejected certain of the pending claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over selected claims of U.S. Pat. Appl. No. 11/192,923, filed July 29, 2005, or U.S. Pat. Appl. No. 11/194,342, filed

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still later based on its Serial No. Applicants request that this rejection be held in abeyance until one of the applications matures into a patent.

4. No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicant respectfully requests reconsideration of the above claims. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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